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Spirocyclic Nonpeptide Glycoprotein IIb–IIIa Antagonists. Part 3: Synthesis and SAR of Potent and Specific 2,8-Diazaspiro[4.5]decanes

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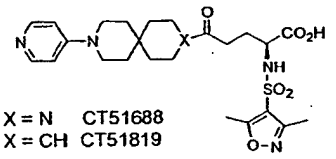
Abstract—The synthesis and biological activity of analogues containing spiro piperidinylpyridine and pyrrolidinylpyridine templates are described. The potent activity of these compounds as platelet aggregation inhibitors demonstrates the utility of the spiro structures as central template for nonpeptide RGD mimics.

Over the past several years, potent and selective GPIIb–IIIa antagonists (peptides and nonpeptides) have been identified and developed, such as eptifibatide, tirofiban, and abciximab, and are currently being used as intravenous agents in the treatment of acute thrombosis.[1] Efforts to discover orally active GPIIb–IIIa inhibitors with appropriate pharmaceutical properties have also been extensive.[1] As part of a program to identify oral antagonists with improved pharmaceutical properties, we have focused on spirocyclic scaffolds, and have identified 3,9-diazaspiro[5,5]undecane, and 3-azaspiro[5,5] undecanes as constrained central templates suitable for preparing potent, conformationally-limited GPIIb–IIIa antagonists such as CT51688 and CT51819.[2]



Based on our initial success with these templates we have also explored the 6,5-spirocyclic system such as the 2,8-diazaspiro[4.5]decane template for its potential in obtaining potent orally active GPIIb–IIIa antagonists.

The focus of the current study was to evaluate two new series of 6,5-diazaspirocyclic containing templates (Fig. 1) with basic and acidic pharmacophore groups alternately attached to five- and six-membered ring amines.

The synthesis of the 2,8-diaza-8-(4-pyridyl)-spiro [4.5]decane (piperidinylpyridine nucleus) and its isomer, the 2,8-diaza-2-(4-pyridyl)spiro[4.5]decane (pyrrolidinyl

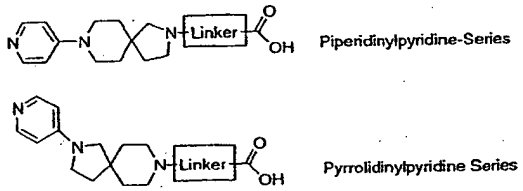
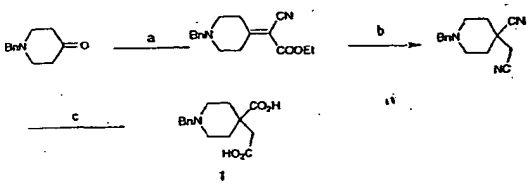


Figure 1. The 2,8-diazaspiro[4.5]decane series.



Scheme 1. Synthesis of dicarboxylic acid **1**: (a) ethyl cyanoacetate, Et_3N, CH_2Cl_2, rt; (b) KCN, EtOH–H_2O, reflux, 18 h; (c) concd HCl, reflux, 24 h.

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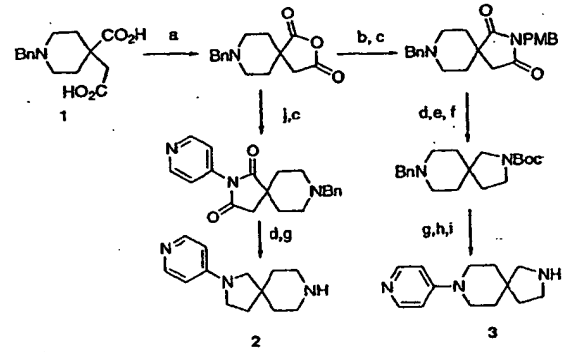
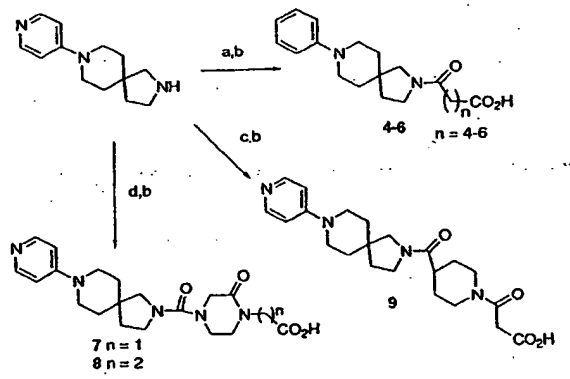
pyridine nucleus) are shown in Schemes 1 and 2.[3] Our first goal was to explore the optimal distance and type of linkage between the pyridyl and carboxylate functionalities. These templates were coupled to various carboxylic acid bearing segments via amide and urea linkages, following the protocols described in Schemes 3, 4, 5, and 7. In general, the amide-linked analogues were synthesized by reacting the tricyclic-spirocyclics with either suitably protected carboxylic acids (via peptide coupling), or with acid chlorides to provide compounds **4–9**, **27–32**, and **36–38** (Schemes 3, 7, and 8). The urea-linked analogues were synthesized by reacting the spirocyclics with either corresponding isocyanates, or *p*-nitrophenylcarbamates; for example, compounds **7–8** (Scheme 3), and compounds **11–16** (Scheme 5).

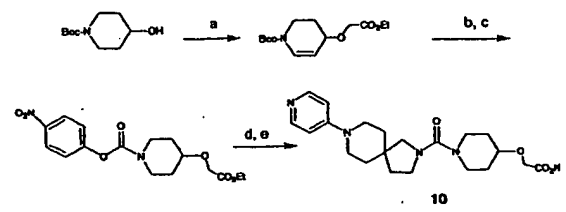
To determine whether more rigid conformational restrictions within the linker would further modulate the activity of antagonists, the linear carboxylic acid linkers were substituted with several rigid cyclic, and aryl-acid units (Schemes 5 and 7). The syntheses of these rigid linkers, bearing the required carboxylic acid functionality,



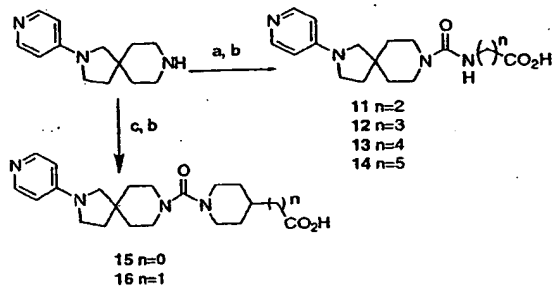
Scheme 2. Synthesis of 2,8-diaza-8-(4-pyridyl)spiro[4.5]decane, and 2,8-diaza-2-(4-pyridyl)spiro[4.5]decane: (a) $SOCl_2$. (b) *p*-methoxybenzyl amine, DIEA, CH_3CN, rt; (c) NaOAc, Ac_2O, reflux; (d) BH_3/THF, reflux; (e) CAN, 5% H_2O, CH_3CN; (f) $(Boc)_2O$, NaOH, dioxane; (g) $Pd(OH)_2/C$, MeOH, 100 psi H_2; (h) 4-bromopyridine, $Pd_2(dba)_3$, S-BINAP, *t*-BuONa, toluene, 95 °C; (i) 50% TFA, CH_2Cl_2; (j) 4-aminopyridine, DIEA, DMF, 100 °C.



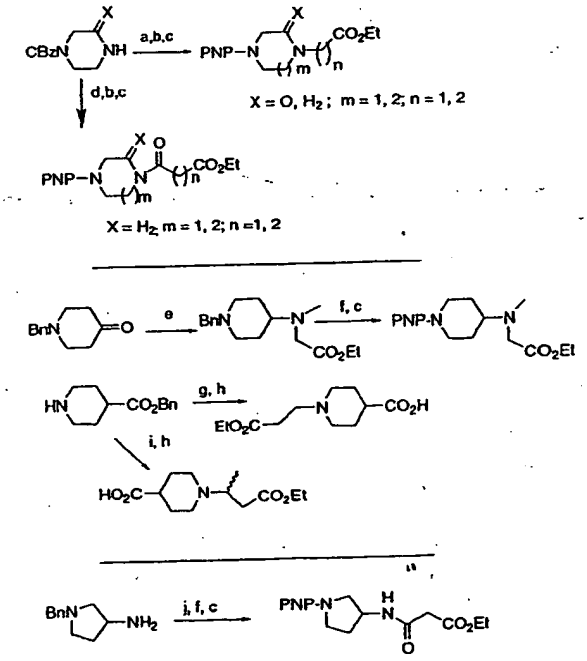
Scheme 3. Synthesis of analogues containing 2,8-diaza-8-(4-pyridyl)spiro[4.5]decane nucleus: (a) $ClCO(CH_2)_{4-6}CO_2Et$, DIEA, DCM; (b) 2 N HCl; (c) 4-(2-ethoxycarbonyl-acetyl)-cyclohexanecarboxylic acid, HOBt, DIEA, DMF; (d) PNP-derivative, DIEA, DCM.



Scheme 4. (a) Ethyldiazoacetate, $\{Rh(OAc)_2\}_2$, fluorobenzene, rt; (b) TFA; (c) 4-nitrophenyl chloroformate, DIEA, CH_2Cl_2, rt; (d) tricyclic piperidine hydrochloride, DIEA, DMF, 70 °C; (e) 2 N HCl, rt.



Scheme 5. General synthesis of analogues containing 2,8-diaza-2-(4-pyridyl)spiro[4.5]decane nucleus: (a) PNP–$NH(CH_2)_nCO_2Et$, DIEA, DCM; (b) 2 N HCl; (c) *p*-nitrophenyl (PNP)-derivative.

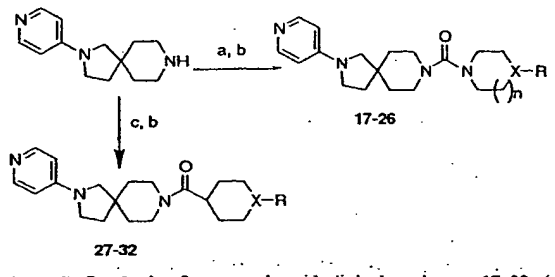


Scheme 6. Synthesis of carboxylic acid segments: (a) NaH, DMF, $Br(CH_2)_nCO_2Et$; (b) $Pd(OH)_2/C$, EtOH, 50 psi H_2; (c) *p*-nitrophenyl chloroformate, DIEA, DCM; (d) $ClCO(CH_2)_nCO_2Et$, DIEA, DMF; (e) sarcosine ethyl ester, $NaB(OAc)_3H$, AcOH, DCM; (f) 10% Pd/C, 100 psi H_2; (g) $Br(CH_2)_2CO_2Et$, DIEA, DCM; (h) 10% Pd/C, 1 atm H_2; (i) ethyl acetoacetate, $NaB(OAc)_3H$, AcOH, DCM; (j) ethyl malonyl chloride, DIEA, DCM.

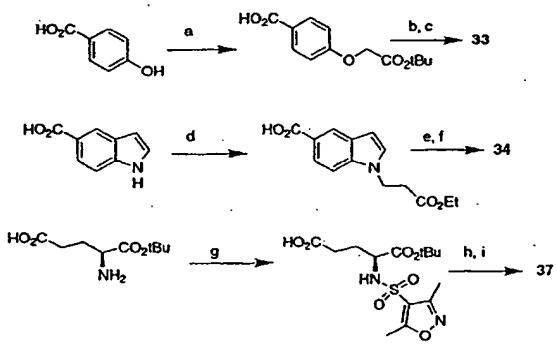
are shown in Scheme 6. Appropriately protected 2-piperazinone, piperazines, pyrrolidines, were alkylated or acylated, then deprotected and converted to the required reactive synthons, *p*-nitrophenyl carbamates. The carboxylic acid moieties required for analogues **19** and **29** were synthesized using the previously described procedures.[2] These segments were then coupled with the spirocyclic units via amide and urea linkages (Schemes 5–8).

As a continuation of our previous work utilizing spirocyclic structures as central template for nonpeptide RGD mimics,[2] we have now investigated the pyridine head-group analogues in the 2,8-diazaspiro-[4.5]-decane class.

Each of the synthesized spirocyclic analogues was assayed for its ability to inhibit the aggregation of ADP-stimulated human platelets and to block the binding of fibrinogen to purified human GPIIb–IIIa. Based on our previous work,[2] we utilized the less basic, direct linked pyridine group in this series of 2,8-diazaspiro[4.5]decanes. In both piperidinyl–pyridine and pyrrolidinyl–pyridine series, with the foremost goal of determining the optimum distance between 'the basic pyridyl nitrogen' and 'the acidic carboxylate functionality'



Scheme 7. Synthesis of urea and amide linked analogues 17–32: (a) PNP-derivative, DIEA, DCM; (b) 2N HCl; (c) carboxylic acids; HOBt, DIEA, DMF.

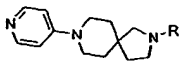


Scheme 8. (a) (i) NaH (2.3 equiv), DMF, 0 °C, 2 h; (ii) bromo *tert*-butyl acetate (1.0 equiv), rt, 20 h; (b) tricyclic piperidine hydrochloride, DIEA, HBTU, DMF; (c) TFA, rt; (d) (i) NaH (2.3 equiv), DMF, 0 °C, 2 h; (ii) bromo ethylacetate (1.0 equiv), rt; (e) tricyclic piperidine hydrochloride, DIEA, HBTU, DMF, rt; (f) 2N HCl, rt; (g) 3,5-dimethylisoxazole-4-sulfonylchloride, 1N NaOH, Na_2CO_3, THF–H_2O; (h) tricyclic piperidinehydrochloride, DIEA, HOBt, CH_2Cl_2, rt; (i) TFA, rt.

normal-chain carboxylic acids of varying lengths were appended to the spirocyclic nucleus via amide linkage. From this initial series, alkyl-linked analogue **5** appeared to exhibit the optimum required distance, but displayed only moderate potency (Table 1).

To determine whether more rigid conformational restriction within the linker would improve further upon the activity, various rigid cyclic linkers were explored. The incorporation of piperazine, piperidine and piperazinone moieties indeed yielded compounds with slight enhancement in activity, compared to the acyclic analogue **5** (Table 2). Analogues **7–10** were significantly more potent in the binding assay than in platelet aggregation, which could well be due to plasma protein binding in the PRP assay, as has also been noted for other GPIIb-IIIa inhibitors.[4]

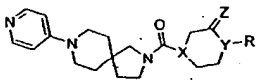
Table 1. In vitro activity of analogues with the piperdinylpyridine nucleus



Compd	R	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
4	$CO(CH_2)_4CO_2H$	>50	80
5	$CO(CH_2)_5CO_2H$	0.043	1.3
6	$CO(CH_2)_6CO_2H$	0.196	18.8

[a]IC_{50} values expressed as the average of at least two determinations. The average error for the determinations was ±15%.

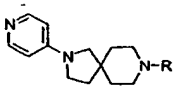
Table 2. Compounds with rigid acidic moiety in 6,5-spiro series



Analogue	R	X	Y	Z	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
7	CH_2CO_2H	N	N	O	0.025	1.18
8	$(CH_2)_2CO_2H$	N	N	O	0.238	8.34
9	$COCH_2CO_2H$	C	N	H_2	0.113	1.58
10	OCH_2CO_2H	N	C	H_2	0.153	1.04

[a]See Table 1.

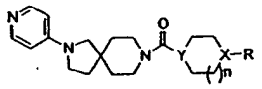
Table 3. In vitro activity of compounds with the pyrrolidinyl–pyridine template



Compd	R	ELISA Fg/GPIIb-IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
11	$CONH(CH_2)_2CO_2H$	28.9	34.6
12	$CONH(CH_2)_3CO_2H$	>50	80
13	$CONH(CH_2)_4CO_2H$	11.9	10.6
14	$CONH(CH_2)_5CO_2H$	>50	74.0

[a]See Table 1.

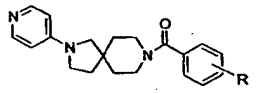
Table 4. Compounds with urea and amide linked rigid acid moiety



Compd	R	X	Y	n	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
15	CO_2H	C	N	1	4.2	55
16	CH_2CO_2H	C	N	1	0.115	1.2
17	OCH_2CO_2H	C	N	1	0.138	3.8
18	$CH_2OCH_2CO_2H$	C	N	1	0.106	2.8
19	$N(Me)CH_2CO_2H$	C	N	1	1.2	12.4
20	CH_2CO_2H	N	N	1	0.252	8.9
21	$(CH_2)_2CO_2H$	N	N	1	0.087	3.2
22	$(CH_2)_2CO_2H$	N	N	2	0.254	3.7
23	$COCH_2CO_2H$	N	N	1	0.136	0.68
24	$COCH_2CO_2H$	N	N	2	0.025	0.70
25	$CO(CH_2)_2CO_2H$	N	N	1	1.5	24.1
26	$NHCOCH_2CO_2H$	C	N	0	0.447	5.9
27	$COCH_2CO_2H$	N	C	1	0.004	0.26
28	$SO_2CH_2CO_2H$	N	C	1	0.090	1.1
29	$CH_2CH_2CO_2H$	N	C	1	0.017	1.0
30	$CH(Me)CH_2CO_2H$	N	C	1	0.225	3.3
31	CH_2CO_2H	N	C	1	0.320	9.5

[a]See Table 1.

Table 5. Compounds with rigid aromatic carboxylic acid moiety in 5,6-spirocyclic series



Compd	R	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
32	*m*-OCH_2CO_2H	0.873	18.3
33	*p*-OCH_2CO_2H	0.688	11.3

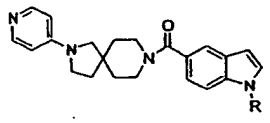
[a]See Table 1.

The other series of analogues that we have investigated involves the direct-linked pyrrolidinyl–pyridine template, since this template, although isomeric to the previous one, would be expected to exist in a different conformation. In this series, the straight alkyl-chain linked analogues, **11–14** (Table 3), exhibited diminished inhibitory activity in both the binding and aggregation assays, compared to **5**.

However, when rigid-linkers were utilized, with both the urea and amide attachments, a much more profound enhancing effect on the potency was observed for several of the analogues **15–31** (Table 4), compared to the small enhancement in activity observed for compounds **7–10** in the piperidinyl–pyridine series (Table 2). Most of these analogues displayed ca. 30- to 100-fold potency enhancement in PRP assay, and ca. 500-fold enhancement in the binding assay, relative to the acyclic analogues, **11–14** (Table 3).

By contrast, rigid aryl-acid linked analogues (**32**, **33**, and **34**) displayed only modest potency (Tables 5 and 6), with the exception of the indoleacetic acid derivative **35** which exhibited submicromolar and nanomolar activity

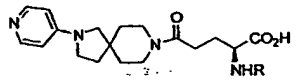
Table 6. Compounds with rigid heteroaromatic carboxylic acid moiety



Compd	R	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
34	$(CH_2)_2CO_2H$	1.80	23.3
35	CH_2CO_2H	0.047	0.95

[a]See Table 1.

Table 7. In vitro activity for compounds with α-substitution



Compd	R	ELISA Fg/GPIIb–IIa IC_{50} (μM)[a]	Human PRP IC_{50} (μM)[a]
36	CBz	0.025	4.1
37	SO_2-isoxazol-4-yl	0.002	0.27
38	CO_2Butyl	0.017	4.0

[a]See Table 1.

in the aggregation and binding assays, respectively (Table 6). Also, the incorporation of α-amino substitution within the carboxylic acid segment in acyclic analogues was found to significantly enhance the activity. Compounds **36–38** (Table 7) exhibit 20- to 400-fold more potency than **11–14** (Table 3).

Incorporation of the 3,5-dimethylisoxazol-4-yl sulfonamide functionalty (analogue **37**) displayed 300-fold potency enhancement in the platelet aggregation assay and 1000-fold more potent in the binding assay relative to its unsubstituted analogue **11** (Table 3). The compound **37** (CT51810), a [5,6]-spirocyclic, is a ring-contracted version of the potent [6,6]-spirocyclic analogue CT51688.[2] Incorporation of this specific sulfonamide residue has been shown previously also to yield extremely potent, tight-binding GPIIb–IIIa antagonists.[2,5] The α-amino substituted analogue **37** is 10-fold less potent in platelet aggregation assays compared to the corresponding [6,6]-spirocyclic analogues CT51688 and CT51819 in [6,6]-azaspiro series. All the active compounds described here were found to have IC_{50} values >100 μM against $\alpha_v\beta_3$ and thus are highly selective inhibitors of GPIIb–IIIa.

The two most potent analogues **27** and **37**, were further studied in vivo in Sprague–Dawley rats, both as free acid, and as their ethyl ester prodrugs. The calculated oral bioavailability following oral and iv administrations (1 mg/kg) of **27** was 10% with a $t_{1/2}$ 0.98 h.

The oral bioavailability of its ethyl ester prodrug of **27** was surprisingly less (5.5%). The oral bioavailability of **37** was 12% with a plasma $t_{1/2}=0.38$ h, and that of its

ethyl ester prodrug ≤5%. In summary, highly active GPIIb–IIIa inhibitors containing the 2,8-diazaspiro[4.5] decane scaffold as a new template have been discovered. However, the marginal pharmacokinetic propertics of these compounds preclude their further development.

References and Notes

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